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Current management of limited-stage SCLC and CONVERT trial impact: Results of the EORTC Lung Cancer Group survey*

Antonin Levy[a,b,*], Lizza E.L. Hendriks[c], Cécile Le Péchoux[a], Sally Falk[d], Benjamin Besse[b,e], Silvia Novello[f], Anne-Marie C. Dingemans[c], Baktiar Hasan[g], Martin Reck[h], Thierry Berghmans[i], Corinne Faivre-Finn[d], On behalf of the EORTC Lung Cancer Group (EORTC LCG)

[a] Department of Radiation Oncology, Gustave Roussy, Institut d'Oncologie Thoracique (IOT), INSERM U1030 Molecular Radiotherapy, Université Paris-Saclay, F-94805, Villejuif, France
[b] Univ Paris Sud, Université Paris-Saclay, F-94270, Le Kremlin-Bicêtre, France
[c] Department of Pulmonary Diseases, GROW - School for oncology and developmental biology, Maastricht University Medical Center+, Maastricht, the Netherlands
[d] The University of Manchester, Division of Cancer Sciences, The Christie NHS Foundation Trust, Manchester, United Kingdom
[e] Department of Medical Oncology, Gustave Roussy, Institut d'Oncologie Thoracique (IOT), Gustave Roussy, Université Paris-Saclay, F-94805, Villejuif, France
[f] Oncology Department, University of Turin, AOU San Luigi, Orbassano (TO), Italy
[g] European Organisation for Research and Treatment of Cancer, Brussels, Belgium
[h] LungenClinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany
[i] Department of Intensive Care and Oncological Emergencies & Thoracic Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

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ABSTRACT

Objectives: The CONVERT trial showed that twice-daily (BD) concurrent chemoradiotherapy should continue to be considered the standard of care in localised LS-SCLC. A survey was conducted to assess the impact of the CONVERT trial in clinical practice and to identify any relevant research questions for future trials in this setting.
Methods and materials: An EORTC Group online survey of LS-SCLC practice was distributed to the EORTC LCG and to members of several European thoracic oncology societies between April and December 2018.
Results: 198 responses were analysed. The majority of respondents (88%, n = 174) were aware of the CONVERT trial. Radiation oncologists comprised 56% of all respondents. Once-daily (OD) radiotherapy is still the most commonly used regimen, however the use of concurrent BD radiotherapy increased after the publication of CONVERT (n = 59/186, 32% prior to and n = 78/187, 42% after the publication, p = 0.053). The main reasons for not implementing BD after the CONVERT publication were logistical issues (n = 88, 44%), inconvenience for patients (n = 56, 28%), and the absence of a statistical survival difference between the two arms in CONVERT (n = 38, 19%). Brain MRI was used by 28% during staging but more than half (60%) of the respondents did not routinely image the brain during follow-up. The main research questions of interest in LS-SCLC were 1) integrating novel targeted therapies-immunotherapies (n = 160, 81%), 2) PCI (+/- hippocampal sparing) vs. MRI surveillance (n = 140, 71%) and, 3) biomarker driven trials (n = 92, 46%).
Conclusion: Once daily radiotherapy (60–66 Gy in 30–33 fractions) remains the most prescribed radiotherapy fractionation, despite the findings suggested by the CONVERT trial.

1. Introduction

Concurrent thoracic chemoradiotherapy (CTRT) is the recommended treatment for limited-stage (LS) small-cell lung cancer (SCLC) patients [1–3]. Hyperfractionated radiotherapy combined with chemotherapy yields better overall survival (OS) compared with standard radiotherapy [4]. However, hyperfractionated radiotherapy schedules have not been widely adopted in routine practice due to limitations in the design of previous studies [4,5], logistical issues and an increase in acute toxicity [6,7]. The CONVERT trial is a multi-centre phase III trial (NCT00433563) that randomly assigned LS-SCLC patients, with Eastern Cooperative Oncology Group performance score 0–2, to receive either twice-daily (BD; 45 Gy in 30 fractions) or once-daily (OD; 66 Gy in 33 fractions) radiotherapy starting with the second

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* Corresponding author at: Department of Radiation Oncology, 114 rue E Vaillant, Gustave Roussy, F-94805, Villejuif, France.
E-mail address: antonin.levy@gustaveroussy.fr (A. Levy).

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cycle of chemotherapy [8]. Prophylactic cranial irradiation (PCI) was given if indicated. Survival outcomes did not differ between BD and OD CTRT (median OS 30 vs. 25 months, respectively), and was higher than anticipated in both arms. Furthermore, toxicity was similar and lower than expected with both regimens. As the trial was designed to show the superiority of OD radiotherapy and was not powered to show equivalence, BD radiotherapy should continue to be considered the standard of care in this setting. However, the impact of the CONVERT trial on daily clinical practice is unclear. Our aim was to assess this impact and also to identify relevant research questions for future trials in this setting. Therefore, we conducted a European survey to evaluate current daily practice in good performance status LS-SCLC patients suitable for CTRT.

2. Material/methods

A European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group (LCG) online (Google® form) survey of LS-SCLC practice was distributed between April and December 2018 to the EORTC LCG and to members of several European thoracic oncology societies. The survey was anonymous and strictly confidential. The questionnaire was divided into five sections: physician's demographic data, thoracic CTRT, PCI, diagnostic and follow-up investigations and future research questions. The survey consisted of 27 questions (5 with "tick box" response options), and was designed to be completed in approximately 10 min. The survey was reviewed by all EORTC LCG board members (N = 12). A copy of the full survey is available in the **Supporting Information**.

The Fisher exact test was used for dichotomous variables comparison. A two-sided P-value < 0.05 was considered significant.

3. Results

198 responses were analysed: 111 respondents were radiation oncologists (56%), 59 were medical oncologists (30%), and 28 were pulmonologists (14%). Overall, 84% of respondents had > 5 years' experience of treating SCLC. Italy (17%, n = 34), the UK (17%, n = 33), and Spain (16%, n = 31) contributed the most responses. The respondents workplaces were: university hospital (56%; n = 111), general public hospital (25%; n = 49), cancer centre (17%; n = 34), private centre (n = 3) and other (n = 1).

The majority of respondents (88%, n = 174) were aware of the CONVERT trial at the time of completing the survey and 21% (n = 42) had included patients in the trial. Concurrent CTRT was considered the standard of care in fit patients (n = 179, 90%) compared to sequential treatment. OD was the most commonly used regimen, but the use of concurrent BD radiotherapy increased after the publication of CONVERT (n = 59/186, 32% prior to and n = 78/187, 42% after the publication, p = 0.053; Table 1). Radiation oncologists preferred BD radiotherapy more often than the other specialties (before CONVERT: 73% (n = 43/59) versus 27% (n = 16/59), respectively, p = 0.004; after CONVERT: 71% (n = 55/78) versus 29% (n = 23/78), respectively, p = 0.004; no difference according to the type of institution).

Table 1
Type of preferred radiotherapy delivered in the concurrent setting.

		Before CONVERT publication Total = 186* N (%)	After CONVERT publication Total = 187* N (%)
OD		127 (68)	109 (58)
	Preferred regimen	60-66 Gy: 76/127 (60)	60-66 Gy: 72/109 (66)
BD		59 (32)	78 (42)
	Preferred regimen	45 Gy: 58/59 (98)	45 Gy: 78/78 (100)

* excluding respondents that never used concurrent CTRT.

60–66 Gy in 30–33 fractions was the most commonly prescribed OD radiotherapy regimen (n = 76/120, 61%). The main reasons for not implementing BD radiotherapy after the CONVERT publication ("tick all that apply" answer) were logistical issues (n = 88, 44%), inconvenience for patients (n = 56, 28%), and the absence of a statistical survival difference between the two arms in the CONVERT trial (n = 38, 19%). Cisplatin-etoposide was considered the standard chemotherapy regimen in the concurrent CTRT setting by 92% (n = 182) of respondents. 77% (141/182) reported delivering 4 cycles and 23% (41/182) deliver 6 cycles of chemotherapy. G-CSF (granulocyte colony-stimulating factor) was used by 39%, either routinely or as secondary prophylaxis.

Regarding the staging investigations routinely carried out before CTRT, 163 (83%) reported using positron emission tomography-computed tomography (PET-CT) and 129 (65%) brain magnetic resonance imaging (MRI). Furthermore, 55 (28%) used brain computed-tomography and 14 (7%) did not image the brain at all.

With regards to follow-up and response evaluation, chest computed tomography (CT) was the most commonly used imaging modality (95% (n = 189) and 94% (n = 186), respectively). Only 14% (n = 29) followed up patients with PET-CT. More than half (60%, n = 118) of the respondents did not routinely image the brain during follow-up. Of the 80 respondents who reported imaging the brain, MRI (45%, n = 36/80) was used less frequently than CT scans (55%, n = 44/80). PCI was routinely used in patients who had not progressed after CTRT (n = 187, 94%). The most commonly prescribed PCI dose was 25 Gy in 10 fractions (n = 158, 80%) and more than half of respondents did not apply an upper age limit (n = 104, 53%). The median upper age limit was 75 years (47/94: 50%; range 65–81 years) for the other 94 respondents.

The main research questions of interest in LS-SCLC were 1) integrating novel targeted therapies-immunotherapies (n = 160, 81%), 2) PCI (+/- hippocampal-avoidance) vs. MRI surveillance (n = 140, 71%) and, 3) biomarker driven trials to identify patients most likely to benefit from CTRT (n = 92, 46%).

4. Discussion

This European survey, designed to evaluate the impact of the CONVERT trial publication on routine practice showed that the use of BD radiotherapy increased after the CONVERT publication (32% prior to and 42% after the publication). A public poll on Twitter organised after CONVERT was published received 143 votes, almost half of which (48%) chose BD over OD radiotherapy. This poll also suggested that the results of the CONVERT trial are influencing oncologists' opinions [9]. Another analysis reported that BD radiotherapy increased after the 2000s (21% after vs. 8% before) [6]. However, despite evidence from randomised trials, OD remains the most prescribed radiotherapy fractionation. In this analysis, the main reasons for not implementing BD were due to logistical issues (44%), inconvenience for patients (28%), and the absence of a statistical survival difference between the two arms of the CONVERT trial (19%, which is a misinterpretation given the superiority trial design).

In an American survey conducted before the CONVERT trial publication, 60% (n = 184) of clinicians preferred administering OD radiotherapy, mainly (130/184: 71%) because it is more convenient for patients [7]. It should however be emphasised that most departments only treat small numbers of LS-SCLC patients each year. The gap between BD fractions is a minimum of 6 h and the treatment is delivered over 3 weeks rather than over 6.5 weeks with OD radiotherapy, making BD radiotherapy a feasible treatment option for patients. BD radiotherapy toxicity has also substantially decreased with modern radiation techniques and smaller volumes of oesophagus are being treated. In the Turrisi study, one third of patients experienced grade 3+ radiation esophagitis compared to < 20% in CONVERT [4,8]. Furthermore, in CONVERT < 5% patients developed G3+ pneumonitis [8].

Our results also show a high level of interest in clinical research for

LS-SCLC. Ongoing trials in LS-SCLC are assessing immune checkpoint inhibitors (81% of respondents were interested in integrating novel targeted therapies-immunotherapies) concurrently with (pembrolizumab, NCT02402920) or after CTRT (durvalumab + tremelimumab, durvalumab, and placebo, NCT03703297; nivolumab and ipilimumab, NCT02046733: STIMULI recently closed prematurely). A recent trial showed a beneficial effect on survival when the immune checkpoint inhibitor atezolizumab was added to chemotherapy in extensive-stage SCLC, indicating that progress is being made in some aspects of the treatment of SCLC [10]. 71% of respondents also expressed an interest in a trial comparing PCI (+/- hippocampal-avoidance) vs. MRI surveillance (71%). In line with the latest European Society for Medical Oncology (ESMO) guidelines [2,3], most respondents used PCI routinely (94%) without upper age limits (53%). Brain MRI is generally used for baseline staging (65%, 28% using brain CT and 7% not imaging the brain at all) but not for follow-up (n = 36/198, 18%). Of note, the risk of developing brain metastases after PCI was the same in both arm of the CONVERT trial [11]. As of early 2019, the cognitive impact of hippocampal-avoidance (HA) PCI in the PREMER-TRIAL (NCT02397733) has been reported in an abstract, where HA-PCI compared to conventional PCI revealed a non-significant decline by ≥ 5 points at HVLT-R total recall score in 28% of the total group [12]. The final results of further studies evaluating brain MRI surveillance and mature results on HA-PCI in LS-SCLC (NCT02635009: NRG CC003; NCT01780675: HA-PCI; NCT02058056: SAKK 15/12) are awaited.

As previously described [13], the inherent limitations of this type of survey include the absence of a known response rate and a potential selection bias. We do not have data on the total number of physicians who received the survey as it was circulated by the national societies. Most respondents were from Western European centres and the networks used to distribute the questionnaire generally targeted a specific population (physician members of scientific societies and those working in teaching hospitals). These groups may have been more likely to participate and be more interested in clinical trials.

SCLC guidelines have not been updated since the publication of the CONVERT trial [2,3]. ESMO and American Society for Radiation Oncology (ASTRO) SCLC guidelines will be published in 2020. A repeat survey of practice should ideally be undertaken after the guidelines have been updated.

5. Conclusion

Once daily radiotherapy (60–66 Gy in 30–33 fractions) remains the most prescribed radiotherapy fractionation, despite the findings suggested by the CONVERT trial.

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Declaration of Competing Interest

Authors declare no conflict of interest and no funding related to this study.

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-Spain SEOR (Spanish Association of Radiotherapy and Oncology)

-Switzerland SAKK (Swiss Group of Cancer Clinical Research)

-UK BTOG (British Thoracic Oncology Group)

-Europe EORTC LCG (European Organisation for Research and Treatment of Cancer Lung Cancer Group)

-ROG (Radiation Oncology Group)

-ERS (European Respiratory Society)

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.08.007.

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